REMARKS

In the Office Action dated May 5, 2006 as clarified by the Advisory Action dated August 25, 2006, the Examiner: (1) rejects claims 1 – 6, 8 and 19 – 37 under 35 U.S.C. § 112, ¶ 1 for an alleged lack of enablement; and (2) rejects claims 1, 6, 8 and 21 – 37 under 35 U.S.C. § 112, ¶ 1 for an alleged lack of written description. On September 5, 2006 Applicants filed a Notice of Appeal. However, in lieu of filing an appeal brief, Applicants have filed a Request for Continued Examination and amended the claim set. Below, Applicants address the Examiner's concerns in view of the amended claim set.

Applicants' invention as reflected in the present claim set

Applicants invention as reflected in the present claim set is directed to methods for selecting siRNA and the development of algorithms that assist in these methods.

Applicants developed methods for selecting siRNA that increase the likelihood that a siRNA will be functional. According to these methods, a siRNA is selected for a given gene by using a rational design, *i.e.*, application of a set of criteria that enhance the probability of identifying a functional siRNA. However, although the claimed methods are advantageous in increasing the likelihood that a siRNA that is selected will be functional, the methods as presently amended contain no limitations that suggest that the use of any particular claimed method will result in a siRNA of a specific functionality.

Claim 1 as amended focuses the at least one criterion on the comparison of the total number of A and U base at the two different ends of the duplex region of a siRNA. More specifically the set of recited criteria comprise comparing the A and U bases among the first and the last, the first two and the last two, the first three and the last three, the first four and the last four, or the first five and last five nucleotides within a duplex. New claims 38 – 42 are species claims that are directed individually to each one of the five criteria.

The criteria described in claim 1 refer to differential thermal stability of the two ends of the duplex regions of the siRNA. As stated on page 31, lines 15 – 19, the inventors observed that a bias toward low internal thermodynamic stability of the duplex at the 5' antisense end is characteristic of naturally occurring miRNA precursors and

invented a selection method to use this insight to increase the likelihood that siRNA that are selected will be functional. Applicants analyzed hundreds of siRNA to develop these criteria.

Moreover, Applicants' specification clearly teaches the importance of these criteria throughout, and a person of ordinary skill could easily use the claimed methods to select a siRNA for a target gene of interest. Specifically, the specification notes, "low 5' (sense strand) AISP [Average Internal Stability Profile] values of strong siRNAs may be necessary for determining which end of the molecule enters the RISC complex." Page 44, lines 9 – 10. The specification further describes how Applicants identified the average internal stability profile of strong siRNA. Page 41, lines 24 – page 44, line 32. These results are illustrated in figure 6b, which demonstrates that the delta G for the first position of the antisense strand (position 1) has a distinctly smaller absolute value than that of the last position of the antisense strand (position 19). This difference between the first and last positions extends for positions 1 - 5 (and 15 - 19), and is easily seen in figure 6(b). As the specification clarifies: "A relative measure of local internal stability is the A/U base pair (bp) content." Page 37, lines 24 –25 of the specification.

Applicants' specification further teaches: "If the duplex has 19 base pairs, those at positions 15 – 19 on the sense strand will unwind first if the molecule exhibits a sufficiently low internal stability." Page 31, line 33 – page 32, line 1; see also page 45, line 33 – page 46, line 4 ("The siRNA functionality was shown to correlate with overall low internal stability of the duplex and low internal stability of the 3' sense end (or differential stability of the 3' sense compared to the 5'sense strand), which may reflect strand selection and entry into the RISC."). Thus, the specification demonstrates the preference for selecting a siRNA that satisfies the recited criteria.

Claim 6 and claims 27 –29, which depend on claim 6, were previously pending. These claims are directed to methods for developing an algorithm. Claim 6 has been amended to remove references to "rationally designed" and functionality. The dependent claims contain minor amendments.

New independent claim 43 is based on previously pending dependent claim 20, which was canceled, but includes elements 3 – 8 and 10 –11 of page 21, line 29 – 22, line 10 as part of a Markush group. Claims 44 – 60 depend on claim 43, and support for

those claims may also be found in the aforementioned passages. As the specification notes "one or more of these criteria" may be use. Page 25, line 26 of the specification.

Response to Enablement Rejection

The Examiner rejected previously pending claims 1 – 6, 8 and 19 – 37 under 35 U.S.C. § 112, ¶ 1 for failing to comply with the enablement requirement. Of these claims, only claims 1, 6 and 27 – 29 are pending. Applicants address the enablement requirement solely with respect to these claims.

The enablement requirement is met if the description "'enables any mode of making and using the invention.'" *Johns Hopkins v. CellPro.* 152 F.3d 1342, 1361 (Fed. Cir. 1998) (quoting *Engel Indus., Inc. v. Lockformer Co.,* 946 F.2d 1528, 1533 (Fed. Cir. 1991)). The outstanding enablement rejections are based on the theories that: (i) the application of certain criteria will not produce a siRNA of a desired functionality (Advisory Action at p. 3); (ii) the criteria recited in previously pending claims 2 and 19 do not represent a proven set of criteria as required for the rational design for siRNA (Advisory Action at p. 4); and (iii) undue experimentation would be necessary to produce a functional or hyperfunctional siRNA (Advisory Action at page 5). With respect to the first and third bases, Applicants respectfully submit that because none of the claims recite limitations directed to functionality or employ the language "rationally designed," the rejection should not be maintained. *Ex parte Chen,* 61 U.S.P.Q.2d 1025, 1029 (Bd. Pat. App. Interf. 2001) (enablement rejection not proper when not directed to claim limitation). With respect to the second basis, Applicants have canceled claims 2 and 19 thereby rendering moot that basis for rejection. Applicants reserve the right to prosecute all canceled claims in one or more continuing applications.

Applicants also submit that the detailed specification provides, and the large number of examples demonstrates, that the claims are enabled. For example, claim 1 and claims 38 – 42, which depend on claim 1, are directed to generating a set of siRNA, applying the criterion of more A/U bases at the 5'end of the antisense region than at the 3' end of the antisense region. Table III identifies 270 different siRNA derived from cyclophilin B, the diazepam binding inhibitor (DBI) and the luciferase gene. (The sense

strands of these duplexes are provided.) By looking at the list, a person of ordinary skill could select one of the three genes, visually look for the siRNA that satisfies the recited criteria and select it. By way of further example, a person of ordinary skill in the art could also examine any of the other approximately 1.6 million sequences disclosed in the application or reported in a publicly available database, examine the two ends of the duplex forming region and evaluate whether the criteria were met.

Further (although not necessary to satisfy the enablement requirement), Applicants have demonstrated the value of this selection criteria using GFP-specific siRNA isolated from *N. benthamiana.* See page 44, lines 15 – 32, and example 6b.

Claims 6 and 27 – 29 are directed to methods for generating algorithms. The specification describes the steps that can be employed to generate these algorithms at for example, page 30, line 18 – page 32, line 19; page 34, line 34 – page 36, lines 9. Examples of formulas generated by this techniques are Formulas I – IX. See page 24, line 17 – page 25, line 31; page 28, line 17 – page 30, lines 15.

Claims 43 – 60 are directed to methods for selecting siRNA based on the satisfaction of at least one or more of the recited criterion. Applicants note that none of these claims contain a limitation directed to selecting a siRNA of any particular functionality. Instead, the claims are directed to applying the criteria and selecting siRNA that satisfy the recited criteria.

By way of example the recited criteria are contained within the various formulas, Formulas I- IX, and these formulas have been used to generate over one and one-half million sequences that have an increased likelihood of being functional when compared to sequences selected at random. Thus, the specification more than amply demonstrates how to select a siRNA using these criteria. See e.g., example I, applying formula VII to sort siRNA, wherein SEQ. ID. 0032 satisfies the criteria A_{19}; example V, identifying the application of algorithm VIII to generate SEQ. ID. NO. 301, which satisfies A_{19}. Table V listing over one hundred siRNA; Example VII describing, of how to apply these criteria to the entire genome. Accordingly, a person of ordinary skill could easily select the ones that do.

As noted above, the criteria within the claims are specifically identified on page 21, line 26 – page 23, line 5, wherein the specification recites that any one or more of

them may be used. Further, Table IV (page 40, lines 1 – 23) demonstrates the value of these criteria. See also page 38, line 18 – page 39, line 32.

Based on the foregoing, Applicants respectfully submit that the pending claims are enabled by the specification. If the Examiner continues to disagree that any of the claims are not enabled, Applicants respectfully request that the Examiner identify which of the recited limitations she believes are not enabled.

Response to Written Description Rejection

The Examiner rejected previously pending claims 1, 6, 8 and 21 – 37 under 35 U.S.C. § 112, ¶ 1 for failing to comply with the written description requirement. Of these claims, only claims 1, 6 and 27 –29 are pending. Applicants address the written description requirement with respect to only these claims.

The written description requirement dictates that the specification must describe the claimed subject matter in a way that one skilled in the art can recognize what is claimed. 35 U.S.C. § 112; *University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 923 (Fed. Cir. 2004). When an Examiner basis a rejection on this basis, she bears the burden of making a prima facie case of unpatentability and must show "'evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.'" *In re Alton,* 37 U.S.P.Q.2d 1578, 1553 (Fed. Cir. 1996) (quoting *In re Wertheim,* 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976)).

In previous communications, the Examiner has advanced two broad theories as to why the claims are not supported by the specification: (1) "the instant claims are not limited to the non-target specific criteria set forth in the specification"; and (2) "the claims are considered to lack a sufficient written description regarding the application of a 'proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA.'" (Advisory Action page 6) For at least two reasons, Applicants respectfully submit that these bases for rejection are inappropriate with respect to the currently pending claims.

First, the currently pending claims all recite limitations that are provided in the specification, including with respect to the recited criteria or variables. Claim 1 is supported by page 31, line 33 – page 32, line 1; page 37, lines 24 – page 38, line 2; page

41, line 24-page 46, line 4. For at least the reasons that claim 1 satisfies the written description requirement, claims 38 – 42 satisfy it as well. Claim 6 recites specific variables that may be considered in developing the algorithm. These limitations are described at page 8, lines 16-28, page 34, line 34 – page 41, line 22. For at least the reasons that claim 6 satisfies the written description requirement, claims 27 – 29 satisfy it as well. Claim 43 is similar to previously pending claim 20, which the Examiner has already recognized as being supported by the specification when she did not reject it in the Advisory Action. Further, this claim is supported by page 21, line 32; page 24, line 13-page 25, line 31; page 29, line 17-page 30, line 16; page 40, lines 1-23. Accordingly, claim 43 satisfies the written description requirement. For at least the reasons that claim 43 satisfies the written description requirement, claims 44 – 60 satisfy it as well.

Second, the Examiner asserted, "the claims are considered to lack a sufficient written description regarding the application of a 'proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA.'" Applicants respectfully disagree with the Examiner. As Table IV and figure 6b demonstrate Applicants have shown that the claimed criterion and variables are proven (though Applicants do not agree that such a showing was necessary). Moreover, Applicants note that none of the claims contain a limitation that the uses the language of functionality or hyperfunctionality. Accordingly, an alleged lack of support for a limitation that is not recited in the claims is not appropriate. *Moba, B.V. v. Diamond Automation, Inc.,* 325 F.3d 1306, 1319 (Fed. Cir.) (written description requirement asks whether the disclosure supports the claimed invention), *cert. denied,* 540 U.S. 982 (2003); MPEP 2163.04[I] ("In rejection a claims, the examiner must set forth express findings of fact which support the lack of written description . . . . These findings should (A) Identify the claim limitation at issue.").

In view of the amendments and arguments presented above, Applicants respectfully request that the Examiner withdraw the written description rejection.

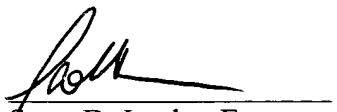
Conclusion

All of the Examiner's rejections having been fully traversed and addressed, Applicants respectfully request allowance of the pending claims.

Applicants submit that no fee is required in connection with the filing of this Amendment and Reply other than the fee for the Request for Continued Examination. If any additional fee is deemed necessary, please charge Deposit Account No. 11-0171.

At this time, Applicants also request a telephonic interview with the Examiner. A copy of form PTOL-413A accompanies this communication.

Respectfully submitted,



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